Srivastava's Group at Molecular Biophysics Unit, IISc-Bangalore

Anand Srivastava

B. Tech, IIT - Kharagpur, India
PhD, The Ohio State University, Columbus
Post-doctoral fellowship, University of Chicago
Email: anand@iisc.ac.in

Research Interest: We develop and use multiscale theories and molecular simulations tools and apply ideas/concepts from statistical mechanics and condensed matter physics to understand the behavior of complex biological systems. Our primary focus is in the field of membrane biophysics. Specific research directions include:

1. Membrane Spatiotemporal Organization: Plasma membrane is a complex self-assembly of a variety of lipids, sterols and proteins. Differential molecular interactions among these diverse constituents give rise to spatial and dynamic heterogeneities in the membrane structure. These sub-100 nm transient structures, which are stabilized far away from equilibrium, are believed to be functionally important in various physiological processes of the cell ranging from cell growth and movement to signal transduction and intercellular transport of proteins. Using advance molecular simulations techniques and ideas/concepts from statistical mechanics and condensed matter physics, we are trying to address a few fundamental questions in the field of membrane spatiotemporal organization. This includes exploring the evolutionary rationale behind maintaining such complex lipid diversity despite the high metabolic expense of lipid homeostasis and identifying the build-in degeneracy in the membrane organization vis-à-vis related functionalities.

2. Probing intermediates in vesicular transport: Biological membranes undergo dramatic changes in curvature/shape during process such as endocytosis, infection, immune response, the formation of organelles and division. These dynamic vesicular transport processes are often accompanied by tightly regulated leakage-free membrane fusion/fission reactions. Though topologically reversed, both reactions require that two bilayers are brought in close proximity against very high activation (hydration) energy barriers and possibly pass through several non-bilayer intermediates. The coupling between the conformation changes in the protein machinery and the orderly rearrangements of lipids leads to extreme membrane remodeling. The experimental difficulties associated with capturing the short-lived intermediates in protein conformations and membrane topologies point to the requirement for high-fidelity multiscale simulations. Currently, we are exploring the molecular mechanisms underlying the dynamin-assisted fission and Env-mediated HIV-1 fusion processes. We plan to apply the tools developed in the lab to explore the sub-millisecond kinetics and intermediates in complex vesicular transport processes such as those found in Golgi and Endoplasmic Reticulum.

3. Force-induced conformation changes: In vivo mechanical forces, much like biochemical and electric signals, possess distinguishable features (magnitude, frequency, mode (steady/pulsatile), type (laminar/turbulent), orientation and duration), which can be diagnosed by specific biological machinery. Gating processes in ion-channels and activation of focal adhesion (FA) proteins at the cell-matrix interface are some examples of stress-activated systems of interest for us. The force-induced conformational changes are intrinsically non-equilibrium in nature and non-trivial to model. Currently, we are using large-scale molecular simulations with advance-sampling techniques to understand the polymodal gating behavior in TREK subfamily of the two-pore domain (K2P) Potassium channels.

People:

1. Madhusmita Tripathy (Postdoctoral Scholar, DBT fellowship)
Dr. Tripathy received her B.Sc. with Physics Honors in 2005 from Utkal University, Bhubaneswar. She completed her M.Sc. in Physics with a specialization in Solid State Physics in 2009 from the same university. She performed her doctoral research at the Department of Physics, Indian Institute of Technology Madras, under the supervision of Prof. P. B. Sunil Kumar and Prof. Abhijit P. Deshpande. Her doctoral work focused on the development of systematic coarse-graining methodologies for macromolecular systems. She received her PhD. in Physics in 2016 following which, she joined Srivastava Group at Molecular Biophysics Unit, Indian Institute of Science Bangalore. Currently she is working in the field of protein and membrane biophysics.

Research Interests: I am interested in studying the biophysical aspect of allostery in proteins and dynamic heterogeneity in biological membrane. Allosteric proteins are a special class of functional proteins where substrate binding at one part of the protein leads to an activation or inhibition of ligand binding at a distal site. I am interested in the physical origin behind this 'action at a distance' mechanism. Toward this I employ analytical models based on principles of amorphous physics and use Monte Carlo simulations and numerical characterization techniques. Another field of my current research is dynamic heterogeneity in biological membranes. Specifically, I study model lipid membranes with co-existing liquid phases and develop tools to characterize the ordered/disordered lipid domains therein. I also study the structural peculiarity of these domains, such as lipid packing defects, which play a very crucial role in the recruitment of peripheral proteins.

2. Rajeswari Appadurai (Postdoctoral Scholar, DST NPDF fellowship)
Dr. Appadurai received her B.Sc (2005) Madurai Kamaraj University and M.Sc (2007) in Biotechnology Alagappa University in Tamil Nadu. She completed her Ph.D. in Computational Biophysics in 2017 from the Indian Institute of Technology Madras. During her doctoral studies, she worked on the molecular basis of drug resistance and uninterrupted function of HIV Protease employing molecular dynamics simulations and network analyses. Currently, she is an SERB-National post-doctoral fellow in the Srivastava Group at the Indian Institute of Science-Bangalore, where she is working in the field of biophysical characterization of mechanosensitive ion channels.

Research Interests: My research interests are focused on understanding the intrinsic dynamics and force-induced conformational changes in channel proteins. I am interested in delineating the intricate signaling pathways by which the mechanical signal propagates from the membrane to the channel pore by employing multi-scale molecular dynamics simulations and network analyses. Besides sensing the mechanical stimuli, some of the MSCs are also capable of responding to various other stimuli such as temperature, pH, etc. I am interested in capturing the delicate balance in the conformational equilibrium underlying such polymodal action of proteins using experimental and computational biophysical techniques. I also study how the heterogeneity in the cell membrane alters the rate of key cellular processes such as conformational changes in proteins.

3. Sahithya S. Iyer (Ph.D Student, Started August 2015)
Sahithya Iyer received her MSc degree in Integrated Chemistry from Pondicherry University in 2015. She joined Srivastava group in Autumn 2015 and currently works on understanding the molecular driving forces in sub-100nm membrane organization.

Research Interests: Broadly, I am interested in understanding the complexity in cell membrane organization and in processes such as membrane fusion in HIV virus. In the course of my PhD, I am taking up smaller projects that address these problems, using computational and statistical mechanics tools, one piece at a time. Ultimately, I would like to create a framework through which the complexity and degeneracy in the cellular membrane can be understood with more clarity.

4. Kirtika Jha (Ph.D Student, Started August 2016)
Kirtika Jha received her Bachelors in Biotechnology in 2013 from Patna University and Masters in Biotechnology in 2015 from Jawaharlal Nehru University, New Delhi. She joined the Srivastava group in Autumn 2016 and currently working on developing coarse-grained models for fission proteins.

Research Interest: I am interested in understanding the molecular mechanism behind fission processes during vesicular transport. I am particularly interested in investigating the role of dynamin protein in membrane endocytosis and I am currently working on the development of coarse-grained model for Dynamin. I am using Elastic Network Model (ENM) approach where the protein is modeled as a set of nodes connected through a network of elastic springs.

5. Krishnakanth Bharatam (Ph.D Student, Started August 2017)
Krishnakanth received his Integrated Masters in Biology (specialization in systems biology) in 2015 from University of Hyderabad. He joined the Srivastava group in Autumn 2017 and currently works on incorporating low-resolution experimental data to drive molecular dynamics simulation.

Research interests: My interests include understanding the function of biological macro-molecules in terms of their structure and dynamics, RNA modeling using coarse grained models, employing techniques of molecular dynamics and monte-carlo to understand thermodynamics and kinetics in biological systems.

6. Subasini Thangamani (Junior Research Fellow)
Subasini Thangamani is a final year B. Tech student in Bioinformatics in 2018 from SASTRA University. She has interned in the Srivastava group in 2016 and 2017 summers and is currently doing final year project in his lab where she is working on "Three Dimensional Structure Prediction of Long Non-Coding RNAs Using Integrative Modeling: HOTAIR as a Case Study"

Research Interests: I am interested in the area of RNA computational biology with primary focus on long non-coding RNAs. I am particularly interested in developing a model to predict three-dimensional structure of lnc RNAs and study RNA folding behavior and dynamics using advanced molecular modeling techniques such as coarse-graining and free energy minimization to elucidate the molecular mechanisms behind lnc RNA functions.

Keywords: Membrane Biophysics, Mechanotransduction, Statistical mechanics of Biological Systems, Integrative Modeling

Selected Publications:

1. Iyer, S.S., Tripathy, M. and Srivastava, A. (2018) Characterizing the Liquid-liquid Phase Co-existence in Biomembrane: Insights from Local Non-affine Deformation and Topological Rearrangements (Accepted May 2018, Biophysical Journal)

2. Pak, A.J., Grime, J.M.A., Sengupta, P., Chen, A.K., Durumeric, A.E.P., Srivastava, A., Yeager, M., Briggs, J.A.G., Lippincott-Schwartz, J. and Voth, G.A. (2017) Immature HIV-1 lattice assembly dynamics are regulated by scaffolding from nucleic acid and the plasma membrane. *PNAS*, **114**, E10056-E10065.

3. Kotyada, C., Maulik, A., Srivastava, A. and Singh, M. (2017) Mechanistic Insights into the Differential Catalysis by RheB and Its Mutants: Y35A and Y35A-D65A. *ACS Omega*, **2**, 6691-6702.

4. Srivastava, A. and Voth, G.A. (2014) Solvent-Free, Highly Coarse-Grained Models for Charged Lipid Systems. *Journal of Chemical Theory and Computation*, **10**, 4730-4744.

5. Srivastava, A. and Voth, G.A. (2013) Hybrid Approach for Highly Coarse-Grained Lipid Bilayer Models. *Journal of Chemical Theory and Computation*, **9**, 750-765.

6. Simunovic, M., Srivastava, A. and Voth, G.A. (2013) Linear aggregation of proteins on the membrane as a prelude to membrane remodeling. *PNAS*, **110**, 20396-20401.

7. Lai, C.-L., Srivastava, A., Pilling, C., Chase, A.R., Falke, J.J. and Voth, G.A. (2013) Molecular Mechanism of Membrane Binding of the GRP1 PH Domain. *Journal of Molecular Biology*, **425**, 3073-3090.

News & Notables:

March 2018: Sahithya wins EMBO fellowship to attend the "International Workshop on Biological Membranes: Tiny Lipids With Grand Functions; Helsinki, Finland, 19 - 22 August 2018". Kirtika and Anand also attending the workshop.

March 2018: Sahithya wins poster award at the 42nd Annual Meeting of Indian Biophysical Society at IISER-Pune.

February 2018: Anand presents the work on titled "Pleckstrin-homology domain (PHD) activity in dynamin mediated fission: Molecular-level Insights from Multiscale modeling" in a discussion meeting on "Recent Advances on Molecular Simulations (RAMOLAS 2018)" held at IISc-Bangalore (Feb 8-11, 2018).

January 2018: Madhu received her postodoctoral fellowship from Department of BioTechnology (DBT-India) for her proposal titled "Protein as an Evolvable Functional Material"

December 2017: Anand presents the work on non-affine measurements on biological membrane at the Complex Fluids Meeting (CompFlu2017, Dec 16-19, 2018) at IIT-Madras. The title of the talk was "Physical mechanisms of micro- and nano-domain formation in bio-membranes: Insights from local topological rearrangements and non-affine deformations in lipids"

December 2017: Sahithya is one of the two winners in the "Student Oral Presentation Competition" at the 5th European Joint Theoretical/Experimental Meeting on Membranes (EJTEMM2017), which took place at University in Krakow, Poland from 6th to 8th December 2017.

March 2017: Rajeswari is awarded the national postdoctoral fellowship (NPDF-SERB) from the Department of Science and Technology for her proposal titled "Molecular Determinants of Mechanotransduction at Lipid – Protein and Protein – Protein Interfaces of Mechanosensitive Ion Channels"

December 2016: Anand receives a 3-year early career grant from the Department of Science and Technology for his proposed work titled "Lipid-protein interplay: Computational approaches to characterize the time-dependent spatial and dynamical heterogeneities and their fluctuations during protein-mediated deformation in membranes"

Teaching:

1. DB 201 (Aug 2:0): Mathematics and Statistics for Biologists
Instructors: Supratim Ray, K. Sekar and Anand Srivastava **(6-8 wks)**

a. (Supratim Ray) Calculus: functions, limits & continuity, differentiation/integration
b. (K. Sekar) Linear Algebra: vectors, matrices, determinants, linear equations
c. (Anand Srivastava) Statistics: elements of probability theory, discrete and continuous distributions, measures of central tendency, variability, confidence intervals, formulation of statistical hypotheses, tests of significance

2. MB206 (Aug 3:0): Conformational & structural aspects of biopolymers
Instructor. Instructors: N. Srinivasan and Anand Srivastava (**(8-10 weeks)**

Structure and conformation of biological molecules. Molecular scales driving forces behind higher order structural organization of proteins, lipids and nucleic acids

3. MB 211 (January 3:1): Advance Sampling Methods in Biomolecular Simulations
Instructor: Anand Srivastava **(16 weeks)**

Theoretical and computational aspects of various advance sampling and free energy calculation methods (maximum work theorem, Jarzinsky equality, umbrella sampling, replica exchange, metadynamics, markov state model, etc). Continuum representation of solvent and calculation of electrostatics and non-electrostatics component of solvation free energy. Method development and application of multiscale coarse graining methods such as force-matching, elastic network models, Inverse Boltzmann's and relative entropy methods.